Letter to the Editor

Pancreatitis as a novel complication of aspirin therapy in patients with aspirin-exacerbated respiratory disease

To the Editor:

Aspirin-exacerbated respiratory disease (AERD), previously termed Samter triad, is an adult-onset disease characterized by asthma, hyperplastic chronic sinusitis, nasal polyposis, and hypersensitivity to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Although the upper and lower airway inflammation seen in patients with AERD is exacerbated by the ingestion of aspirin and other NSAIDs, the disease progresses independently of exposure to these medications. Since 1922, when this syndrome was originally identified by Widal,[1] and 1967, when it was further described by Samter and Beers,[2] the clinical efficacy of aspirin desensitization and ongoing aspirin therapy has been well established.[3] Aspirin desensitization is a procedure whereby patients receive increasing doses of aspirin, usually to a dose of 650 mg, over 2 to 3 days. If these patients continue to take aspirin on a daily basis after the desensitization procedure, many of them demonstrate improved control of their asthma and sinus disease.

Chronic aspirin therapy can result in adverse drug reactions in a minority of patients with AERD, with gastrointestinal involvement being the most common. Berges-Gimeno et al[3] evaluated 172 aspirin-desensitized subjects, 24 (14%) of whom had to discontinue aspirin therapy because of side effects: 14 had epigastric pain, 2 had gastrointestinal bleeding, 2 had bleeding from the nose and ear, and 6 had aspirin-induced urticaria. The majority of the gastrointestinal reactions in patients with AERD receiving chronic aspirin are presumed to be either gastritis or peptic ulcer disease, with the former being considered the most common cause. Stevenson and colleagues reported the incidence of gastritis as 18.5% of 65 such patients in their 1990 study[4] and 13.6% of 75 different patients involved in their 1996 report.[5] However, the patients with gastrointestinal side effects were not extensively studied in regard to the cause of their gastrointestinal distress, and the diagnosis of gastritis in these studies seems to have been made clinically. Although pancreatitis is listed as a rare complication of chronic NSAID use,[6] there is no known association between pancreatitis and aspirin therapy in patients with AERD. We describe 3 cases of previously unreported pancreatitis as the cause of abdominal distress during or after aspirin desensitization.

The first of these patients is a 55-year-old man who presented with a several-year history of chronic sinusitis and nasal polyposis requiring 2 sinus surgeries, adult-onset asthma, and sensitivity to aspirin and other NSAIDs. On several occasions, NSAID ingestion had caused marked worsening of nasal congestion, exacerbation of his asthma, and severe epigastric pain, which had been attributed to gastroesophageal reflux disease. At presentation, the patient's systemic medications included omeprazole, glucosamine, montelukast, and simvastatin. During the first day of the patient's aspirin challenge/desensitization, he had his typical reaction after the 325-mg aspirin dose. Although his respiratory symptoms responded to inhaled bronchodilators and anticholinergics, intravenous corticosteroids, and intravenous H_1/H_2 antihistamines, his severe epigastric pain progressed and was accompanied by intense cramping and nausea. He had no diarrhea, vomiting, hives, or hypotension. He was admitted to the hospital, where he was found to have an increased lipase level of 425 U/L (normal, 13-63 U/L) and radiographic evidence of pancreatic inflammation but no gallstones or gallbladder sludge on abdominal computed tomography (CT). He was given a diagnosis of pancreatitis and was ordered to take nothing by mouth, with improvement over the next few days. Other common causes of pancreatitis were excluded, including drugs, alcohol, hypercalcemia, hypertriglyceridemia, infection, and biliary tract disease. He did not complete the desensitization procedure, and his lipase level normalized to 55 U/L on repeat testing several days later when asymptomatic.

Our second patient is a 59-year-old man with a history of AERD who came to our clinic for a repeat aspirin desensitization procedure. A year prior, he had undergone aspirin desensitization at an outside clinic. On the first day of the previous desensitization, he had a respiratory reaction typical of his respiratory symptoms after NSAID exposure, including increasing upper and lower airway symptoms with a documented decrease in FEV_1. He underwent the second day of this initial desensitization without difficulty. Although he did not have any gastrointestinal symptoms on either day of the procedure, he began complaining of severe epigastric pain and nausea the next day. These symptoms persisted for 3 straight days, at which point he was given a clinical diagnosis of gastritis, instructed to discontinue his aspirin therapy, and prescribed a daily proton-pump inhibitor. He improved gradually with this regimen but was not fully asymptomatic from a gastrointestinal standpoint for several weeks. After a year of proton-pump inhibitor therapy with no recurrence of his gastrointestinal symptoms, the patient decided to attempt aspirin desensitization again because both his asthma and sinus disease had become difficult to control and he was needing frequent oral steroids. At this point, systemic medications included only the following over-the-counter supplements: DHEA, omega-3, and a multivitamin. During day 1 of his repeat aspirin challenge, the patient again exhibited a respiratory reaction with a documented decrease in FEV_1 but no gastrointestinal complaints. Shortly after discharge, however, he began to complain of severe epigastric pain, nausea, and vomiting in addition to further worsening of his asthma. He eventually went to the emergency department, where he was given albuterol nebulizer treatments and intravenous corticosteroids for his asthma, as well as antiemetics and pain medications for his gastrointestinal complaints. In addition, he was given a diagnosis of pancreatitis based on an increased lipase level of 789 U/L (normal, 13-63 U/L), hospitalized, and ordered to take nothing by mouth. After an overnight stay, his symptoms improved, and he was discharged on a bland diet. His lipase level the morning after his reaction was 128 U/L, and both amylase and lipase levels were normal at 75 U/L (normal, 30-110 U/L) and 37 U/L, respectively, by later that afternoon. He had an abdominal ultrasound that showed gallbladder sludge but no gallstones. Other causes of pancreatitis, such as drugs, alcohol, and hypercalcemia, were excluded.

Our third patient, a 74-year-old woman, also had pancreatic inflammation after her aspirin desensitization procedure but with a somewhat more subacute presentation than in the first 2 cases. She also had a clinical history classic for AERD and tolerated her

challenge without gastrointestinal complaints. Her systemic medications at the time included cetirizine, clopidogrel, montelukast, vitamin D_3, rosuvastatin, and alendronate. Four days after starting high-dose aspirin therapy at a dose of 650 mg twice daily, she experienced abdominal pain. However, the patient did not mention the discomfort until her follow-up visit 3 weeks later, at which point amylase and lipase measurements were taken and found to be increased at 152 U/L (normal, 30-110 U/L) and 207 U/L (normal, 16-63 U/L), respectively. Her aspirin dose was decreased to 81 mg daily, and she was hospitalized for several days to undergo extensive testing, which included laboratory work, an abdominal CT scan, and both an upper and lower endoscopy, the results of which were within normal limits except for her increased pancreatic enzyme levels. Of particular note, the patient did not have evidence of gallbladder sludge or gallstones on her CT scan. Her abdominal pain improved with the lower aspirin dose, and follow-up amylase and lipase measurements taken 6 weeks later had normalized at 56 and 27 U/L, respectively.

Several case reports have been published describing pancreatitis as a result of aspirin use in conjunction with statins,[7] but there are no previous reports of pancreatitis complicating aspirin challenges or desensitization procedures in patients with AERD. Although the first and third patients were receiving chronic statin therapy at the time of their procedures, which could have contributed to their pancreatic inflammation, the second patient was not. The development of pancreatic inflammation in all 3 patients only after aspirin challenge/desensitization suggests that pancreatitis might be a complication of this procedure in patients with AERD. More importantly, pancreatitis might be the actual cause of abdominal discomfort in some of the patients with AERD who complain of gastrointestinal side effects rather than gastritis or peptic ulcer disease, which are commonly implicated because they are recognized side effects of aspirin therapy. For our 3 patients, the development of pancreatitis might relate to the marked increase in leukotriene levels during aspirin desensitization from an already high predesensitization level, as is typical of patients with AERD.[5] The connection between acute pancreatitis and leukotrienes has been suggested by several animal models. One murine model using sodium taurocholate to induce pancreatitis led to increased levels of several leukotrienes.[8] When cerulein is used to induce pancreatitis, knockout mice lacking the 5-lipoxygenase enzyme crucial for leukotriene synthesis have less pancreatic inflammation and tissue injury, neutrophil infiltration, and adhesion molecule expression compared with mice that do not lack 5-lipoxygenase.[9] Using this same model in rats, blocking the effects of leukotrienes at the level of their receptors has been shown to decrease pancreatic inflammation.[10] Interestingly, all 3 patients received a dose of montelukast before aspirin challenge, and the first and third patients were taking montelukast on a chronic basis at the time of the challenge. This suggests that the leukotriene receptor antagonism provided by montelukast is incomplete and might be insufficient to block the effects of leukotrienes in this subset of patients with levels of leukotrienes and leukotriene receptors that are high at baseline and increase further during the aspirin challenge. Ultimately, however, the mechanism of pancreatitis in these patients is not yet understood, and the role of leukotrienes is just a theoretical construct at this point.

Although our observations relate to just 3 cases, the temporal association between aspirin desensitization and the onset of gastrointestinal distress with normal hepatic panels but evidence for pancreatic inflammation suggests that pancreatitis, although possibly rare, might be a previously unrecognized complication of aspirin desensitization. In addition, the third patient described here raises the possibility that pancreatitis might be a dose-dependent complication of aspirin challenge and long-term aspirin therapy because decreasing her aspirin dose ultimately led to resolution of her abdominal discomfort and normalization of her pancreatic enzyme levels. As in all cases of pancreatitis, secondary causes, such as gallbladder disease, must be ruled out, and the possibility of idiopathic pancreatitis always exists. These 3 cases exhibit a strong temporal association that would be difficult to explain based on gallbladder pathology or chance alone. Until now, cases of pancreatitis during or shortly after aspirin desensitization have likely been classified erroneously as gastritis, given the relatively high prevalence of gastritis in chronic users of high-dose aspirin or other NSAIDs.[11] To better elucidate the association between pancreatic inflammation and aspirin desensitization in patients with AERD, we will prospectively examine the effect of high-dose aspirin on the pancreas in patients with AERD undergoing desensitization. On the basis of these 3 cases, the authors recommend that patients with AERD who experience gastrointestinal symptoms either during their aspirin desensitization procedure or days after and those patients with AERD with underlying pancreatic disease should have their pancreatic enzyme levels monitored.

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